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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002951995 for a patent by ALCHEMIA PTY LTD as filed on 11 October 2002.

WITNESS my hand this
Twenty-third day of October 2003

J. Billingsley

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TEAM LEADER EXAMINATION
SUPPORT AND SALES

CLASSES OF COMPOUNDS THAT INTERACT WITH GPCRs

FIELD OF THE INVENTION

The invention provides classes of biologically active compounds that interact in a pharmaceutically significant manner with G-Protein Coupled Receptors (GPCRs), pharmaceutical compositions containing such compounds and methods of treatment of humans suffering from a disorder which can be at least partially overcome by the compounds or compositions.

BACKGROUND OF THE INVENTION

The drug discovery landscape has been transformed by the genomics revolution. Advances in the understanding of biomolecular pathways and the roles they play in disease will lead to vast numbers of targets for therapeutic intervention. GPCRs represent the most important collection of therapeutic targets available.

GPCRs are proteins that tranduce signals across a cell membrane. They consist of a single polypeptide chain that threads back and forth seven times across the phospholipid bilayer that forms the cell membrane. The polypeptide chain has a portion inside the cell which form a G-protein coupling domain, and a receptor portion outside or in the cell wall. A signal molecule interacts with the receptor which sends the signal through the membrane wall and the signal causes the G-protein coupling domain to interact with a G protein.

Over 50% of marketed drugs target GPCRs. Whilst the druggable extent of GPCRs numbers some 450 receptors only some 200 GPCRs have been matched with their ligands. Orphan receptors suitable for drug targeting may therefore number in excess of 200 receptors. These are receptors with less than approximately 45% sequence identity to known GPCRs for which ligands have not been identified.

The targets of current GPCR drugs include, pain and inflammation, cancer, metabolic and gastrointestinal, cardiovascular and central nervous system disorders.

There is a continuing demand for new therapeutics, especially as our

understanding of biological processes expands from the genomics revolution. The aforementioned GPCRs are suitable targets for therapeutic intervention due to their roles in such disorders as cancers, obesity and erectile dysfunction.

Considering the rate of generation and nature of the targets currently being deconvoluted by biologists, there is a need for the development of drug candidates, designed in a rational manner to purposely interact with selected targets, such as the GPCRs.

From a drug discovery perspective, carbohydrate pyranose and furanose rings and their derivatives are well suited as templates. Each sugar represents a three-dimensional scaffold to which a variety of substituents can be attached, usually *via* a scaffold hydroxyl group, although occasionally a scaffold carboxyl or amino group may be present for substitution. By varying the substituents, their relative position on the sugar scaffold, and the type of sugar to which the substituents are coupled, numerous highly diverse structures are obtainable.

An important feature to note with carbohydrates, is that molecular diversity is achieved not only in the type of substituents, but also in the three dimensional presentation. The different stereoisomers of carbohydrates that occur naturally or non-naturally, offer the inherent structural advantage of providing alternative, rigid presentation of substituents, to a target's binding site.

GPCR's are known to bind to peptide ligands. Amino acid side chains and isosteres thereof, can be coupled to different sugar cores in a variety of alternate, yet fixed presentations. Consequently, by exploiting the numerous monosaccharide stereoisomers available, the conformally fixed nature of the pyranose ring, and the ability to employ a range of substituents, enhanced affinity and selectivity can be tuned for particular targets.

Employing a related methodology, Hirschmann *et al* (Hirschmann, R., et. al., *J. Am. Chem. Soc.*, 1992, *114*, 9217-9218, US 5,552,534, WO 97/28172, WO 95/11686) synthesised several compounds designed as somatostatin analogues and integrin binders. The methodology employed by Hirschmann relied on protracted, linear, non-combinatorial syntheses,

employed exclusively non-aminated pyranoses, and did not exploit any epimerisation chemistry to allow greater access to structural diversity. Consequently, these compounds and methods are manifestly distinct from this present invention.

We have developed a system that allows the chemical synthesis of highly structurally and functionally diverse derivatised carbohydrate and tetrahydropyran structures, of both natural and unnatural origin. The diversity accessible is particularly augmented by the juxtaposition of both structural and functional aspects of the molecules.

Using the axioms of this drug discovery methodology, we synthesised several novel classes of chemotypes in an effort to develop drug candidates against GPCR targets.

SUMMARY OF THE INVENTION

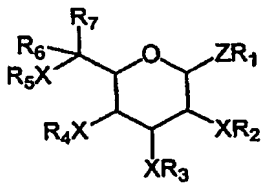
It is a general object of the invention to provide compounds that interact with GPCRs in a biologically significant manner,

It is a further object of the invention to provide a pharmaceutical formulation comprising at least one compound as described herein or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

It is a further object of the invention to provide a method of treatment of a human or animal subject which method comprises administering to the human or animal subject an effective amount of a compound as described herein or a pharmaceutically acceptable salt thereof.

It is a further object of the invention to prepare novel compounds per se.

In one aspect the invention provides for compounds of general formula I, that interact with GPCRs in a biologically significant manner,



General Formula I

Wherein the ring may be of any configuration;

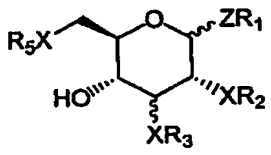
Z is sulphur, oxygen, CH_2, C(O), C(O)HNR^A, NH, NR^A or hydrogen, in the case where Z is hydrogen then R_1 is not present, R^A is selected from the set defined for R_1 to R_5,

X is oxygen or nitrogen providing that at least one X of General Formula I is nitrogen, alternatively X can be an azide, in which case R_1 to R_5 are not present.

R_1 to R_5 are independently selected from the following definition which includes but is not limited to H or an alkyl, acyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituent of 1 to 20 atoms, which is optionally substituted, and can be branched or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted, and

R_6 and R_7 are hydrogen, or may combine to form a carbonyl function.

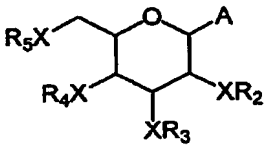
In one embodiment the invention provides for compounds of general formula II that interact with GPCRs in a biologically significant manner,



General Formula II

Wherein R_1, R_2, R_3, R_5, Z and X are defined as in General Formula I.

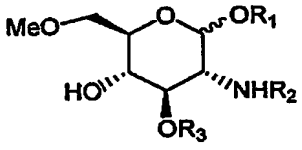
In a second embodiment the invention provides for compounds of general formula III that interact with GPCRs in a biologically significant manner,



General Formula III

Wherein A is defined as hydrogen, SR_1, or OR_1 where R_1 is defined as in General Formula I, and
X and R_2 to R_5 are defined as in General Formula I.

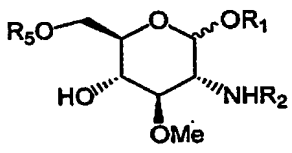
In a preferred embodiment the invention provides for compounds of General Formula IV that interact with GPCRs in a biologically significant manner,



General Formula IV

Wherein R_1-R_3 are defined as in General Formula I.

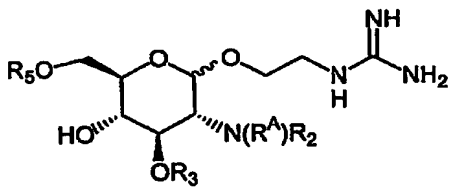
In a second preferred embodiment the invention provides for compounds of General Formula V that interact with GPCRs in a biologically significant manner,



General Formula V

Where in R_1, R_2 and R_5 are defined as in General Formula I.

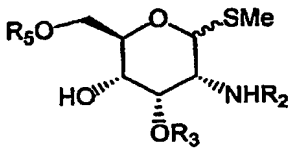
In a third preferred embodiment the invention provides for compounds of General Formula VI that interact with GPCRs in a biologically significant manner,



General Formula VI

Wherein R^A is H or combines with R_2 to form an azide, and
R_3, R_3 and R_5 are defined as in General Formula I.

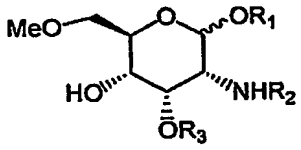
In a fourth preferred embodiment the invention provides for compounds General Formula VII that interact with GPCRs in a biologically significant manner of,



General Formula VII

Wherein, R_2, R_3 and R_5 are defined as in General Formula I.

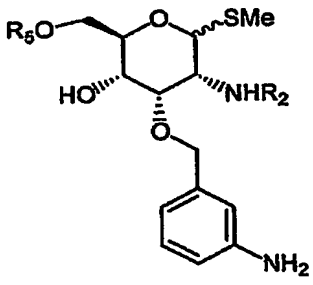
In a fifth preferred embodiment the invention provides for compounds of General Formula VIII that interact with GPCRs in a biologically significant manner,



General Formula VIII

Wherein R_1 to R_3 are defined as in General Formula I.

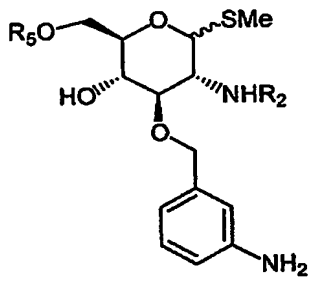
In a sixth preferred embodiment the invention provides for compounds of General Formula IX that interact with GPCRs in a biologically significant manner,



General Formula IX

Wherein R_2 and R_5 are defined as in General Formula I.

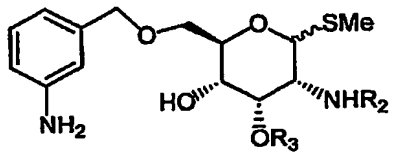
In a seventh preferred embodiment the invention provides for compounds of General Formula X that interact with GPCRs in a biologically significant manner,



General Formula X

Wherein R_2 and R_5 are defined as in General Formula I.

In an eighth preferred embodiment the invention provides for compounds of General Formula XI that interact with GPCRs in a biologically significant manner,

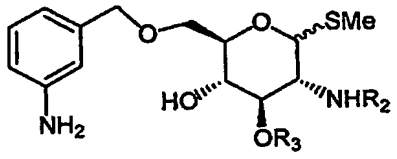


General Formula XI

Wherein R_2 and R_3 are defined as in General Formula I.

In a ninth preferred embodiment the invention provides for compounds of General Formula XII that interact with GPCRs in a biologically significant

manner,

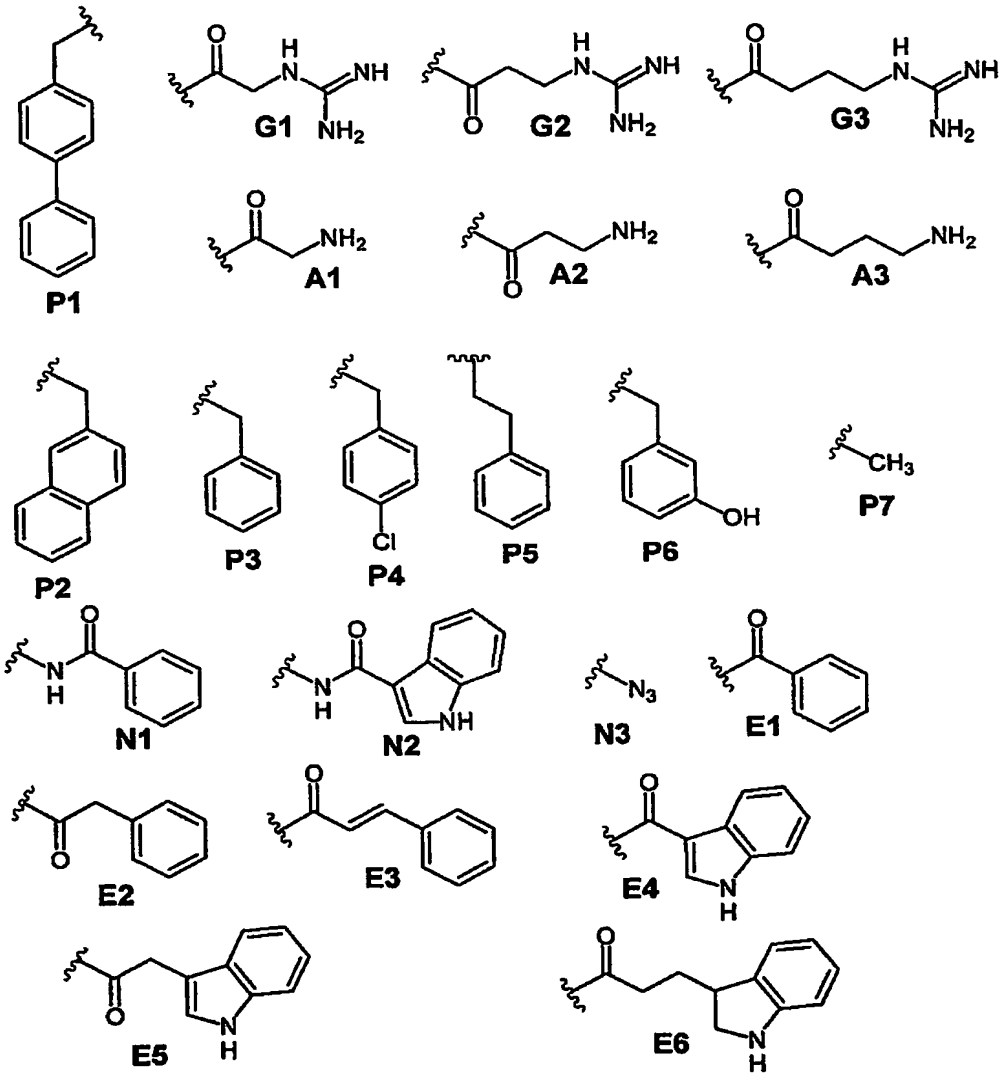


General Formula XII

Wherein R_2 and R_3 are defined as in General Formula I.

Examples of the Invention

Substituents per Example Libraries 1-9

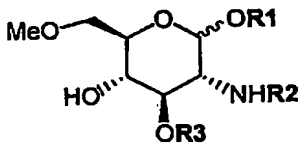


Key

X1 refers to the MC4 receptor assay, X2 refers to the SST5 receptor assay, X3 refer to the CXCR4 receptor assay, and X4 refers to the noradrenalin receptor assay.

A "++" refers to greater than 75% inhibition at 10 micromolar, a "+" refers to greater than 50% inhibition at 10 micromolar and a "-" is considered inactive.

Example Library 1

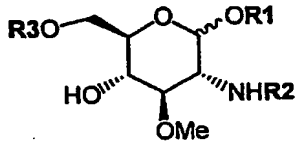


Comp. No.	R1	R2	R3	X1	X2	c LogP
1	P1	G1	P1	+	-	3.56
2	P1	G2	P1	-	-	3.65
3	P1	G1	P2	-	-	2.98
4	P1	G2	P2	-	+	3.07
5	P1	G1	P3	-	-	1.80
6	P1	A3	P3	-	-	2.91
7	P1	G1	P4	-	-	2.44
8	P2	G1	P3	-	-	1.21
9	P2	A3	P3	-	+	2.32
10	P2	G1	P4	-	-	1.86
11	P3	G1	P1	-	-	1.80
12	P3	G2	P1	-	+	1.89
13	P3	A3	P1	-	+	2.91
14	P3	G3	P1	-	+	2.38
15	P3	G1	P2	-	-	1.21
16	P3	G2	P2	-	-	1.30
17	P3	G1	P3	-	-	0.04
18	P3	G2	P3	-	-	0.13
19	P3	A3	P3	-	+	1.14
20	P3	G3	P3	-	-	0.62
21	P3	G1	P4	-	-	0.68
22	P3	G2	P4	-	-	0.77
23	P3	A3	P4	-	+	1.79
24	P3	G3	P4	-	-	1.26
25	P4	G1	P1	-	-	2.44
26	P4	G2	P1	+	+	2.53
27	P4	G2	P2	+	-	1.95
28	P4	G3	P2	-	+	2.44
29	P4	G1	P3	-	-	0.68
30	P4	G2	P3	-	-	0.77
31	P4	A3	P3	-	+	1.79
32	P4	G1	P4	-	-	1.32
33	P4	G2	P4	-	+	1.42
34	P4	G3	P4	-	+	1.91
35	P5	G1	P1	+	-	2.29
36	P5	G2	P1	-	-	2.38

37	P5	G1	P3	-	-	0.53
38	P5	G1	P4	-	-	1.17
39	P1	G2	P6	-	-	1.41
40	P5	G2	P6	-	-	0.14
41	P6	G1	P1	-	-	1.32
42	P6	G2	P1	-	-	1.41
43	P6	G3	P1	-	-	1.90
44	P6	G1	P2	-	-	0.73
45	P6	G3	P2	-	-	1.31
46	P6	G1	P3	-	-	-0.45
47	P6	G2	P3	-	-	-0.35
48	P6	G3	P3	-	-	0.14
49	P6	G1	P4	-	-	0.20
50	P1	G1	P6	-	-	1.32
51	P1	A3	P6	-	-	2.43
52	P1	G3	P6	-	-	1.90
53	P2	G1	P6	-	-	0.73
54	P2	G2	P6	-	-	0.82
55	P2	A3	P6	-	+	1.84
56	P2	G3	P6	-	+	1.31
57	P3	A3	P6	-	-	0.66
58	P3	G3	P6	-	-	0.14
59	P4	G1	P6	-	-	0.20
60	P4	G2	P6	-	-	0.29
61	P4	A3	P6	-	+	1.31
62	P4	A3	P6	-	-	0.78
63	P5	A3	P6	-	-	1.15
64	P5	G3	P6	-	-	0.63
65	P6	A3	P1	-	-	2.43
66	P6	A3	P3	-	-	0.66
67	P6	G2	P4	-	-	0.29
68	P6	A3	P4	-	-	1.31
69	P6	G3	P4	-	-	0.78
70	P1	A3	P1	-	+	4.67
71	P1	G3	P1	++	-	4.14
72	P1	G3	P2	-	+	3.56
73	P1	G2	P3	-	+	1.89
74	P1	G3	P3	-	-	2.38
75	P1	G2	P4	-	+	2.53
76	P1	A3	P4	-	+	3.55
77	P1	G3	P4	+	+	3.03
78	P2	G1	P1	+	+	2.98
79	P2	G2	P1	+	+	3.07
80	P2	A3	P1	-	++	4.08
81	P2	G1	P2	-	-	2.39
82	P2	G2	P2	+	+	2.48

83	P2	A3	P2	+	++	3.49
84	P2	G3	P2	++	+	2.97
85	P2	G2	P3	-	-	1.30
86	P2	G3	P3	-	+	1.79
87	P2	A3	P4	-	++	2.96
88	P2	G3	P4	-	++	2.44
89	P4	A3	P1	-	++	3.55
90	P4	G3	P1	+	+	3.03
91	P4	G1	P2	-	-	1.86
92	P4	A3	P2	-	++	2.96
93	P4	G3	P3	-	-	1.26
94	P5	A3	P1	-	+	3.40
95	P5	G3	P1	-	+	2.87
96	P5	G1	P2	-	-	1.70
97	P5	G2	P2	-	-	1.79
98	P5	A3	P2	-	++	2.81
99	P5	G3	P2	-	-	2.28
100	P5	G2	P3	-	-	0.62
101	P5	A3	P3	-	-	1.63
102	P5	G3	P3	-	-	1.11
103	P5	G2	P4	-	-	1.26
104	P5	A3	P4	-	+	2.28
105	P5	G3	P4	-	+	1.75
106	P1	A3	P2	-	++	4.08
107	P3	A3	P2	-	++	2.32
108	P4	A3	P4	-	++	2.43

Example Library 2

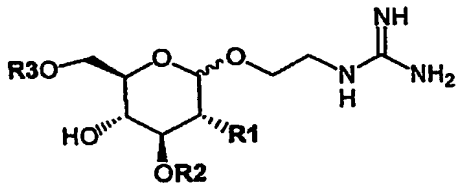


Comp. No.	R1	R2	R3	X1	X2	c LogP
109	P1	G1	P1	++	-	3.56
110	P1	G2	P1	+	-	3.65
111	P1	A3	P1	-	-	4.67
112	P1	G3	P1	+	-	4.14
113	P1	G1	P2	+	-	2.98
114	P1	G2	P2	-	-	3.07
115	P1	A3	P2	++	++	4.08
116	P1	G3	P2	-	-	3.56
117	P1	G1	P3	-	-	1.80
118	P1	G2	P3	-	-	1.89
119	P1	A3	P3	-	-	2.91
120	P1	G3	P3	-	-	2.38
121	P1	G1	P4	+	-	2.44
122	P1	G2	P4	+	-	2.53
123	P1	A3	P4	-	-	3.55
124	P1	G3	P4	+	-	3.03
125	P2	G1	P1	+	-	2.98
126	P2	G2	P1	+	-	3.07
127	P2	A3	P1	+	-	4.08
128	P2	G3	P1	+	-	3.56
129	P2	G1	P2	+	-	2.39
130	P2	G2	P2	+	-	2.48
131	P2	A3	P2	-	+	3.49
132	P2	G3	P2	-	-	2.97
133	P2	G1	P3	-	-	1.21
134	P2	G2	P3	-	-	1.30
135	P2	A3	P3	-	-	2.32
136	P2	G3	P3	-	-	1.79
137	P2	G1	P4	+	-	1.86
138	P2	G2	P4	-	-	1.95
139	P2	A3	P4	-	+	2.96
140	P2	G3	P4	+	-	2.44
141	P3	G1	P1	-	-	1.80
142	P3	G2	P1	-	-	1.89
143	P3	A3	P1	-	-	2.91
144	P3	G3	P1	-	-	2.38
145	P3	G1	P2	-	+	1.21

146	P3	G2	P2	-	-	1.30
147	P3	A3	P2	-	-	2.32
148	P3	G3	P2	-	-	1.79
149	P3	G1	P3	-	-	0.04
150	P3	G2	P3	-	-	0.13
151	P3	A3	P3	-	-	1.14
152	P3	G3	P3	-	-	0.62
153	P3	G1	P4	-	-	0.68
154	P3	G2	P4	-	-	0.77
155	P3	A3	P4	-	+	1.79
156	P3	G3	P4	-	-	1.26
157	P4	G1	P1	+	-	2.44
158	P4	G2	P1	+	-	2.53
159	P4	A3	P1	-	+	3.55
160	P4	G3	P1	+	-	3.03
161	P4	G1	P2	++	+	1.86
162	P4	G2	P2	++	+	1.95
163	P4	A3	P2	++	++	2.96
164	P4	G3	P2	+	-	2.44
165	P4	G1	P3	-	-	0.68
166	P4	G2	P3	-	-	0.77
167	P4	A3	P3	-	+	1.79
168	P4	G3	P3	-	-	1.26
169	P4	G1	P4	-	-	1.32
170	P4	G2	P4	+	-	1.42
171	P4	A3	P4	-	+	2.43
172	P4	G3	P4	+	-	1.91
173	P5	G1	P1	+	-	2.29
174	P5	G2	P1	+	-	2.38
175	P5	A3	P1	+	+	3.40
176	P5	G3	P1	+	-	2.87
177	P5	G1	P2	+	-	1.70
178	P5	G2	P2	+	-	1.79
179	P5	A3	P2	+	+	2.81
180	P5	G3	P2	+	-	2.28
181	P5	G1	P3	-	-	0.53
182	P5	G2	P3	-	-	0.62
183	P5	A3	P3	-	-	1.63
184	P5	G3	P3	-	-	1.11
185	P5	G1	P4	-	-	1.17
186	P5	G2	P4	+	-	1.26
187	P5	A3	P4	-	+	2.28
188	P5	G3	P4	+	-	1.75
189	P1	G1	P6	-	-	1.32
190	P1	G2	P6	-	-	1.41
191	P1	A3	P6	-	-	2.43
192	P1	G3	P6	-	-	1.90
193	P2	G1	P6	-	-	0.73

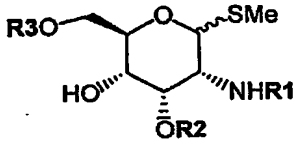
194	P2	G2	P6	-	-	0.82
195	P2	A3	P6	-	-	1.84
196	P2	G3	P6	-	-	1.31
197	P3	G1	P6	-	-	-0.45
198	P3	G2	P6	-	-	-0.35
199	P3	A3	P6	-	-	0.66
200	P3	G3	P6	-	-	0.14
201	P4	G1	P6	-	-	0.20
202	P4	G2	P6	+	-	0.29
203	P4	A3	P6	-	+	1.31
204	P4	G3	P6	-	-	0.78
205	P5	G1	P6	-	-	0.05
206	P5	G2	P6	-	-	0.14
207	P5	A3	P6	-	-	1.15
208	P5	G3	P6	-	-	0.63
209	P6	G1	P1	-	-	1.32
210	P6	G2	P1	+	-	1.41
211	P6	A3	P1	-	-	2.43
212	P6	G1	P2	-	-	0.73
213	P6	G2	P2	+	-	0.82
214	P6	A3	P2	-	-	1.84
215	P6	G3	P2	+	-	1.31
216	P6	G1	P3	-	-	-0.45
217	P6	G2	P3	-	-	-0.35
218	P6	A3	P3	-	-	0.66
219	P6	G1	P4	-	-	0.20
220	P6	G2	P4	-	-	0.29
221	P6	A3	P4	-	-	1.31
222	P6	G3	P4	-	-	0.78

Example Library 3



Comp. No.	R1	R2	R3	X1	X2	X3	c Log P
223	N1	P2	P7	-	-	-	1.49
224	N1	P7	P2	-	-	-	1.49
225	N2	P7	P3	-	-	-	0.38
226	N3	P3	P2	-	-	-	3.11
227	N3	P2	P3	-	-	-	3.11

Example Library 4

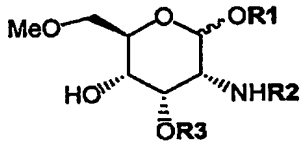


Comp. No.	R1	R2	R3	X1	X4	X2	c LogP
228	A1	P3	P3	-	-	+	0.91
229	G1	P3	P3	+	-	+	0.38
230	A2	P3	P3	+	-	++	1.00
231	G2	P3	P3	++	-	++	0.47
232	A3	P3	P3	-	-	++	1.49
233	G3	P3	P3	+	-	++	0.97
234	A1	P3	P4	-	-	++	1.55
235	G1	P3	P4	++	-	+	1.03
236	A2	P3	P4	-	-	+	1.64
237	G2	P3	P4	+	-	+	1.12
238	A3	P3	P4	+	-	++	2.13
239	G3	P3	P4	++	ND	++	1.61
240	A1	P3	P1	-	-	++	2.67
241	G1	P3	P1	++	ND	++	2.15
242	A2	P3	P1	+	-	+	2.76
243	G2	P3	P1	++	ND	++	2.24
244	A3	P3	P1	+	ND	++	3.25
245	G3	P3	P1	++	-	++	2.73
246	A1	P3	P2	+	-	++	2.08
247	G1	P3	P2	++	-	++	1.56
248	A2	P3	P2	+	-	++	2.17
249	G2	P3	P2	++	-	++	1.65
250	A3	P3	P2	+	-	++	2.67
251	G3	P3	P2	++	-	++	2.14
252	A1	P4	P3	-	-	++	1.55
253	G1	P4	P3	+	-	++	1.03
254	A2	P4	P3	-	-	++	1.64
255	G2	P4	P3	++	-	++	1.12
256	A3	P4	P3	-	-	++	2.13
257	G3	P4	P3	+		++	1.61
258	A1	P4	P4	-	-	++	2.20
259	G1	P4	P4	++	-	++	1.67
260	A2	P4	P4	+	-	++	2.29
262	G2	P4	P4	+	-	++	1.76
262	A3	P4	P4	-	-	+	2.78

263	G3	P4	P4	+	-	++	2.26
264	A1	P4	P1	+	-	++	3.32
265	G1	P4	P1	++	-	++	2.79
266	A2	P4	P1	+	-	++	3.41
267	G2	P4	P1	++	-	++	2.88
268	A3	P4	P1	+	-	+	3.90
269	G3	P4	P1	++	-	+	3.37
270	A1	P4	P2	+	-	+	2.73
271	G1	P4	P2	++	-	+	2.20
272	A2	P4	P2	++	-	++	2.82
273	G2	P4	P2	++	-	++	2.30
274	A3	P4	P2	++	-	++	3.31
275	G3	P4	P2	++	ND	++	2.79
276	A1	P1	P3	+	-	+	2.67
277	G1	P1	P3	++	-	+	2.15
278	A2	P1	P3	-	-	++	2.76
279	G2	P1	P3	+	-	+	2.24
280	A3	P1	P3	-	-	+	3.25
281	G3	P1	P3	+	-	+	2.73
282	A1	P1	P4	-	-	+	3.32
283	G1	P1	P4	++	-	+	2.79
284	A2	P1	P4	++	-	++	3.41
285	G2	P1	P4	++	-	++	2.88
286	A3	P1	P4	-	-	+	3.90
287	G3	P1	P4	++	-	+	3.37
288	A1	P1	P1	+	-	++	4.44
289	G1	P1	P1	+	ND	+	3.91
290	A2	P1	P1	+	-	++	4.53
291	G2	P1	P1	+	-	+	4.00
292	A3	P1	P1	+	-	+	5.02
293	G3	P1	P1	-	ND	++	4.49
294	A1	P1	P2	+	-	-	3.85
295	G1	P1	P2	++	-	+	3.32
296	A2	P1	P2	+	-	+	3.94
297	G2	P1	P2	++	-	+	3.41
298	A3	P1	P2	+	-	++	4.43
299	G3	P1	P2	++	-	++	3.91
300	A1	P2	P3	+	-	+	2.08
301	G1	P2	P3	++	-	+	1.56
302	A2	P2	P3	-	-	++	2.17
303	G2	P2	P3	++	-	++	1.65
304	A3	P2	P3	+	-	++	2.67
305	G3	P2	P3	++	-	++	2.14
306	A1	P2	P4	+	-	+	2.73
307	G1	P2	P4	+	-	+	2.20
308	A2	P2	P4	+	ND	++	2.82

309	G2	P2	P4	++		++	2.30
310	A3	P2	P4	++		++	3.31
311	G3	P2	P4	++		++	2.79
312	A1	P2	P1	++		++	3.85
313	G1	P2	P1	++		++	3.32
314	A2	P2	P1	+		++	3.94
315	G2	P2	P1	++		+	3.41
316	A3	P2	P1	+		+	4.43
317	G3	P2	P1	++		+	3.91
318	A1	P2	P2	+		++	3.26
319	G1	P2	P2	++		++	2.74
320	A2	P2	P2	+		++	3.35
321	G2	P2	P2	++		++	2.83
322	A3	P2	P2	+		++	3.84
323	G3	P2	P2	++		++	3.32

Example Library 5

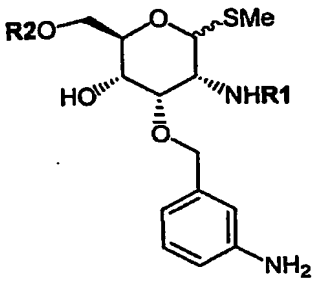


Comp. No.	R1	R2	R3	X1	X4	X2	c LogP
324	P3	A1	P3	-	-	+	0.56
325	P2	A1	P2	-	ND	++	2.91
326	P4	A1	P1	+	-	+	2.97
327	P5	A1	P3	-	-	+	1.05
328	P3	A1	P4	-	-	++	1.20
329	P2	A1	P1	-	ND	+	3.50
330	P4	A1	P4	+	-	+	1.85
331	P2	A1	P4	-	-	+	2.38
332	P3	A1	P1	+	-	++	2.32
333	P5	A1	P4	-	-	+	1.70
334	P2	A1	P3	-	ND	+	1.74
335	P5	A1	P1	-	-	+	2.82
336	P3	A1	P2	-	-	++	1.74
337	P5	A1	P2	+	ND	+	2.23
338	P4	A1	P3	-	-	-	1.20
339	P4	A1	P2	+	-	+	2.38
340	P4	A2	P2	+	-	++	2.47
341	P3	A2	P3	-	-	++	0.65
342	P3	A2	P4	+	-	++	1.30
343	P4	A2	P4	+	-	++	1.94
344	P3	A2	P1	++	-	++	2.42
345	P2	A2	P3	-	-	++	1.83
346	P5	A2	P2	-	-	++	2.32
347	P3	A2	P2	+	-	++	1.83
348	P2	A2	P2	-	ND	++	3.00
349	P5	A2	P1	+	ND	++	2.91
350	P4	A2	P3	-	-	++	1.30
351	P5	A2	P4	++	-	++	1.79
352	P2	A2	P4	-	ND	++	2.47
353	P5	A2	P3	-	-	++	1.14
354	P2	A2	P1	+	ND	++	3.59
355	P4	A2	P1	++	-	++	3.06
356	P3	A3	P2	+	-	++	2.32
357	P5	A3	P2	+	-	++	2.81
358	P4	A3	P3	-	-	++	1.79

359	P2	A3	P3	-	-	++	2.32
360	P2	A3	P4	-		++	2.96
361	P5	A3	P3	-	ND	++	1.63
362	P3	A3	P3	-	-	++	1.14
363	P4	A3	P2	-	-	++	2.96
364	P2	A3	P2	-	ND	++	3.49
365	P4	A3	P1	++	ND	++	3.55
366	P2	A3	P1	+	ND	++	4.08
367	P3	A3	P4	-	-	++	1.79
368	P4	A3	P4	+	-	++	2.43
369	P3	A3	P1	++	-	++	2.91
370	P5	A3	P1	++	ND	++	3.40
371	P5	A3	P4	+	ND	++	2.28
372	P4	G1	P2	++	-	++	1.86
373	P5	G1	P4	++	-	+	1.17
374	P2	G1	P1	++	ND	+	2.98
375	P4	G1	P1	++	-	++	2.44
376	P2	G1	P2	++	ND	++	2.39
377	P5	G1	P3	+	-	-	0.53
378	P2	G1	P3	+	-	+	1.21
379	P3	G1	P2	++	-	++	1.21
380	P4	G1	P4	++	-	++	1.32
381	P4	G1	P3	++	-	++	0.68
382	P5	G1	P1	++	ND	++	2.29
383	P2	G1	P4	++	-	+	1.86
384	P5	G1	P2	++	-	+	1.70
385	P3	G1	P1	++	-	++	1.80
386	P3	G1	P4	++	-	++	0.68
387	P3	G1	P3	+	-	+	0.04
388	P4	G2	P3	+	-	++	0.77
389	P5	G2	P4	++	ND	++	1.26
390	P2	G2	P2	++	ND	++	2.48
391	P5	G2	P1	++	ND	++	2.38
392	P3	G2	P2	++	-	++	1.30
393	P2	G2	P3	+	-	++	1.30
394	P5	G2	P2	+	ND	+	1.79
395	P3	G2	P3	+	-	++	0.13
396	P4	G2	P4	++	-	++	1.42
397	P5	G2	P3	-	ND	+	0.62
398	P3	G2	P1	++	-	++	1.89
399	P4	G2	P1	++	-	++	2.53
400	P2	G2	P1	++	ND	++	3.07
401	P4	G2	P2	++	-	++	1.95
402	P3	G2	P4	++	-	++	0.77
403	P2	G2	P4	++	ND	++	1.95
404	P5	G3	P1	++	ND	++	2.87

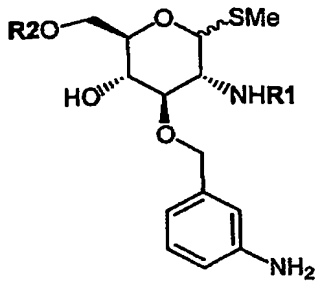
405	P5	G3	P3	+	-	+	1.11
406	P5	G3	P2	++	-	++	2.28
407	P4	G3	P2	++	-	++	2.44
408	P2	G3	P4	++	ND	++	2.44
409	P4	G3	P4	++	-	++	1.91
410	P3	G3	P4	++	-	++	1.26
411	P3	G3	P3	+	-	++	0.62
412	P2	G3	P3	-	-	++	1.79
413	P5	G3	P4	++	-	++	1.75
414	P2	G3	P1	++	ND	++	3.56
415	P3	G3	P1	++	-	++	2.38
416	P4	G3	P1	++	-	++	3.03
417	P3	G3	P2	++	-	++	1.79
418	P4	G3	P3	+	-	++	1.26
419	P2	G3	P2	++	ND	++	2.97

Example Library 6



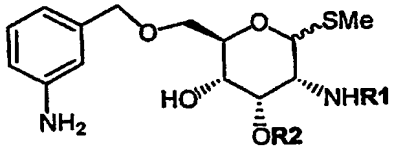
Object Id	R1	R2	X1	X2	c LogP
420	E1	P3	+	++	2.96
421	E1	P4	-	++	3.61
422	E2	P3	-	-	2.77
423	E2	P4	+	+	3.42
424	E3	P3	-	-	3.05
425	E3	P4	-	-	3.69
426	E4	P3	-	-	3.02
427	E4	P4	-	-	3.67
428	E5	P3	-	++	2.83
429	E5	P4	-	-	3.48
430	E6	P3	+	+	3.20
431	E6	P4	-	-	3.84

Example Library 7



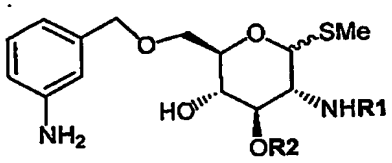
Comp. No.	R1	R2	X1	X2	c LogP
432	E1	P3	-	-	2.96
433	E2	P3	-	-	2.77
434	E3	P3	-	-	3.05
435	E4	P3	-	-	3.02
436	E5	P3	-	++	2.83
437	E6	P3	+	-	3.20
438	E1	P4	-	+	3.61
439	E2	P4	-	-	3.42
440	E3	P4	-	-	3.69
441	E4	P4	+	-	3.67
442	E5	P4	-	+	3.48
443	E6	P4	+	-	3.84

Example Library 8



Comp. No.	R1	R2	X1	X2	c LogP
444	E1	P3	-	+	2.96
445	E2	P3	-	+	2.77
446	E3	P3	-	-	3.05
447	E4	P3	+	-	3.02
448	E5	P3	-	++	2.83
449	E6	P3	-	-	3.20
450	E1	P4	-	++	3.61
451	E2	P4	-	-	3.42
452	E3	P4	-	-	3.69
453	E4	P4	-	-	3.67
454	E5	P4	-	-	3.48
455	E6	P4	++	-	3.84

Example Library 9



Comp. No.	R1	R2	X1	X2	c LogP
456	E1	P3	+	-	2.96
457	E2	P3	+	-	2.77
458	E3	P3	+	-	3.05
459	E4	P3	-	-	3.02
460	E5	P3	+	++	2.83
461	E6	P3	-	-	3.20
462	E1	P4	++	+	3.61
463	E2	P4	+	-	3.42
464	E3	P4	+	-	3.69
465	E4	P4	-	-	3.67
466	E5	P4	+	-	3.48

It should be appreciated that various other changes and modifications can be made to any embodiment described without departing from the spirit and scope of the invention.

Dated this 11th day of October 2002

Alchemia Pty Ltd

By their Patent Attorneys

CULLEN & CO.

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